

Fig. S1. *TGF-stimulated association of eight signaling proteins with the EGF receptor measured using luciferase fragment complementation imaging.* CHO cells stably co-expressing EGFR-NLuc and the CLuc-fused version of one of eight signaling proteins were assayed for TGF-stimulated light production in the presence of luciferin. Cells were stimulated with the indicated concentration of TGF at time  $t=0$  and light production monitored for 25 min.

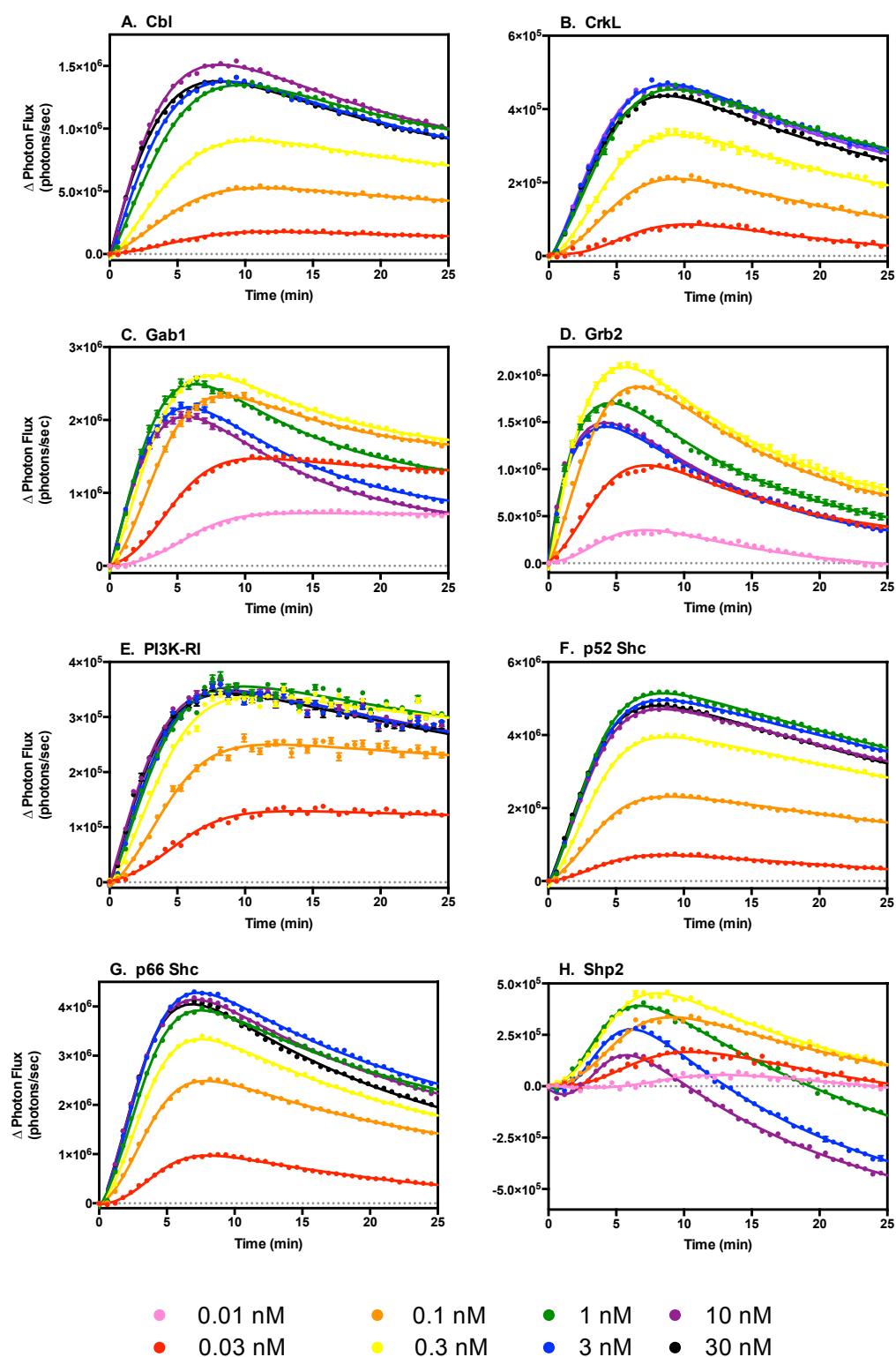


Fig. S2. *BTC-stimulated association of eight signaling proteins with the EGF receptor measured using luciferase fragment complementation imaging.* . CHO cells stably co-expressing EGFR-NLuc and the CLuc-fused version of one of eight signaling proteins were assayed for BTC-stimulated light production in the presence of luciferin. Cells were stimulated with the indicated concentration of BTC at time  $t=0$  and light production monitored for 25 min.

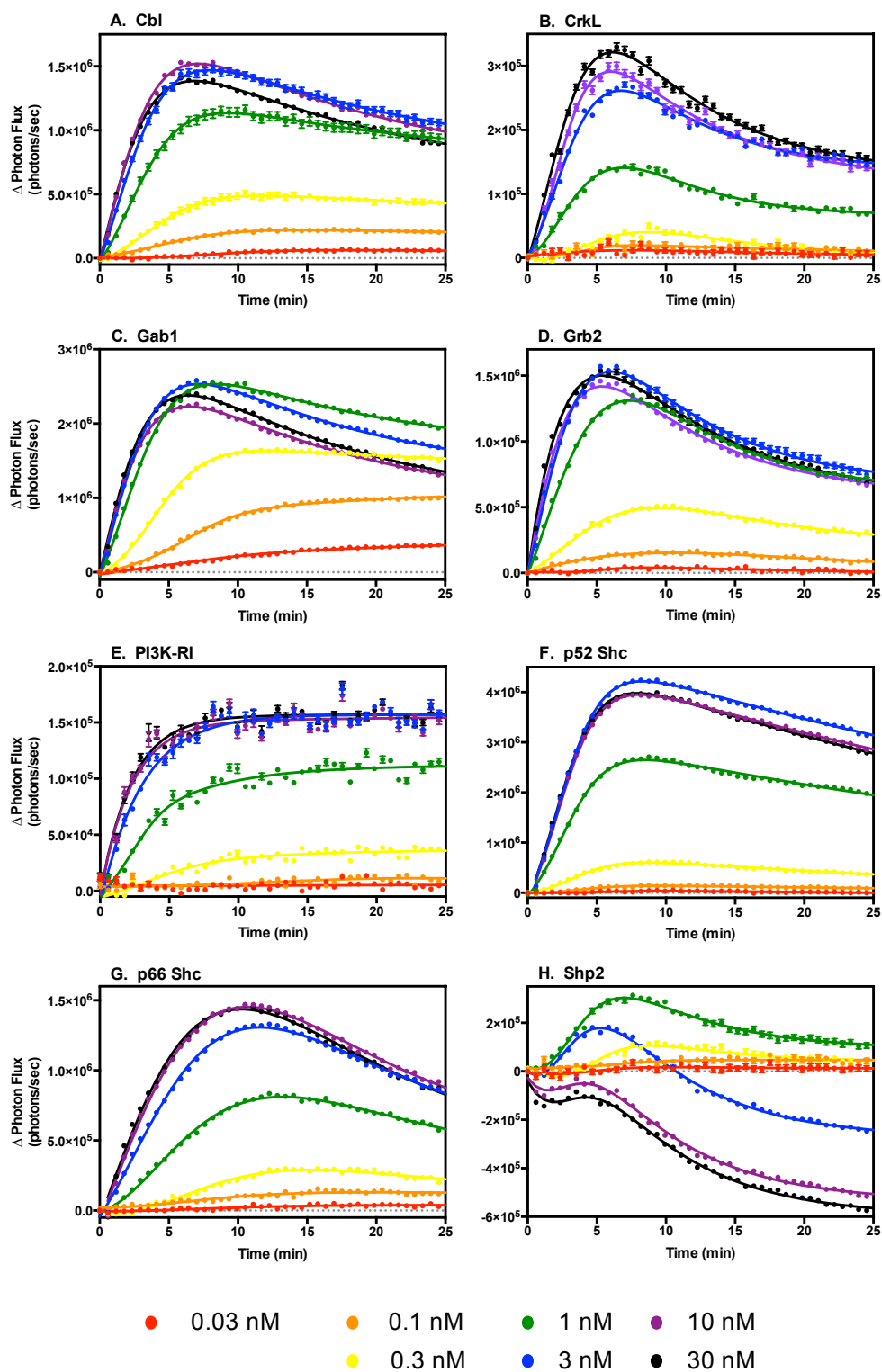


Fig. S3. *HB-EGF-stimulated association of eight signaling proteins with the EGF receptor measured using luciferase fragment complementation imaging.* CHO cells stably co-expressing EGFR-NLuc and the CLuc-fused version of one of eight signaling proteins were assayed for HB-EGF-stimulated light production in the presence of luciferin. Cells were stimulated with the indicated concentration of HB-EGF at time  $t=0$  and light production monitored for 25 min.

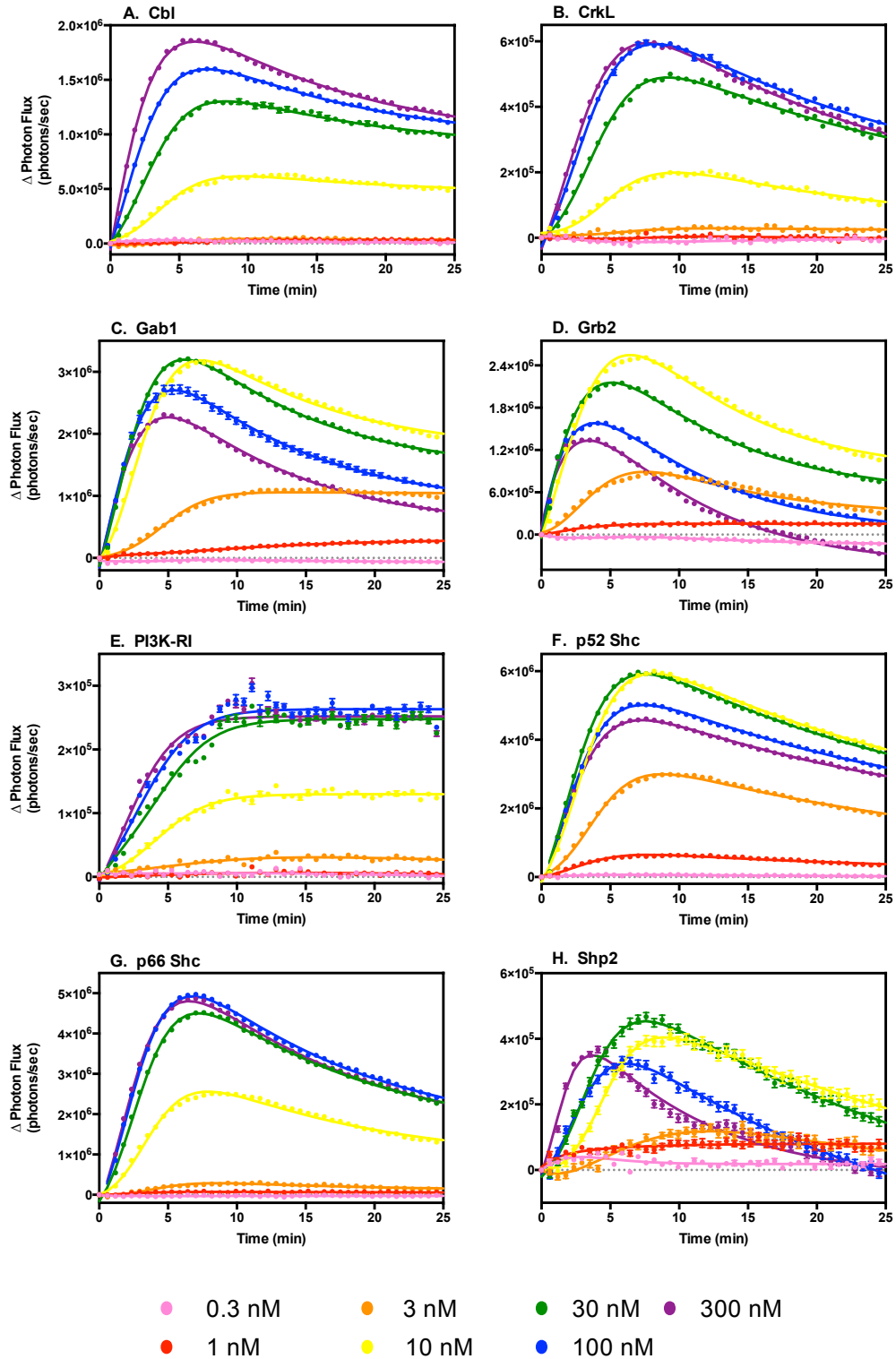


Fig. S4 *AREG-stimulated association of eight signaling proteins with the EGF receptor measured using luciferase fragment complementation imaging.* CHO cells stably co-expressing EGFR-NLuc and the CLuc-fused version of one of eight signaling proteins were assayed for AREG-stimulated light production in the presence of luciferin. Cells were stimulated with the indicated concentration of AREG at time  $t=0$  and light production monitored for 25 min.

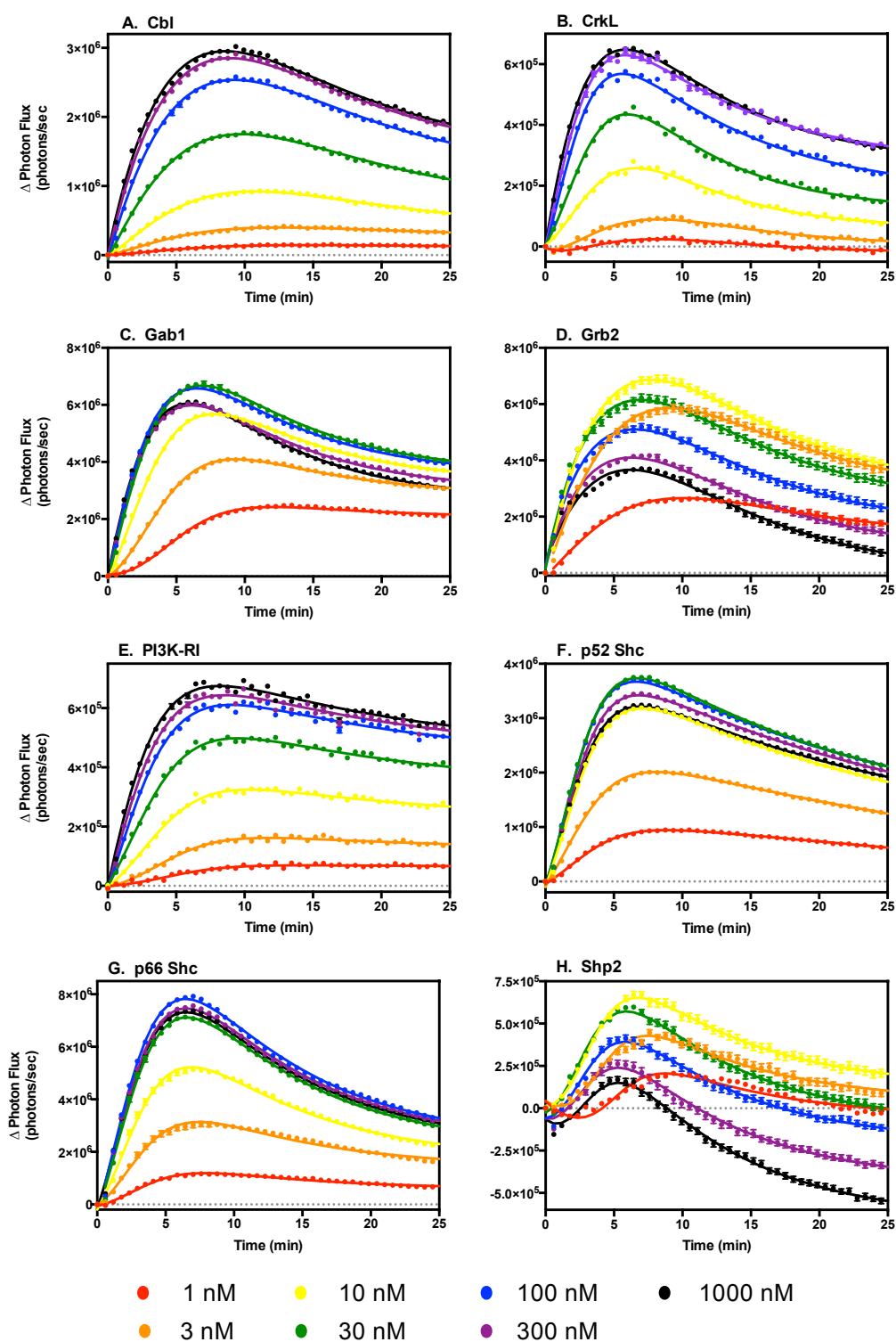


Fig. S5 EPG-stimulated association of eight signaling proteins with the EGF receptor measured using luciferase fragment complementation imaging. CHO cells stably co-expressing EGFR-NLuc and the CLuc-fused version of one of eight signaling proteins were assayed for EPG-stimulated light production in the presence of luciferin. Cells were stimulated with the indicated concentration of EPG at time  $t=0$  and light production monitored for 25 min.

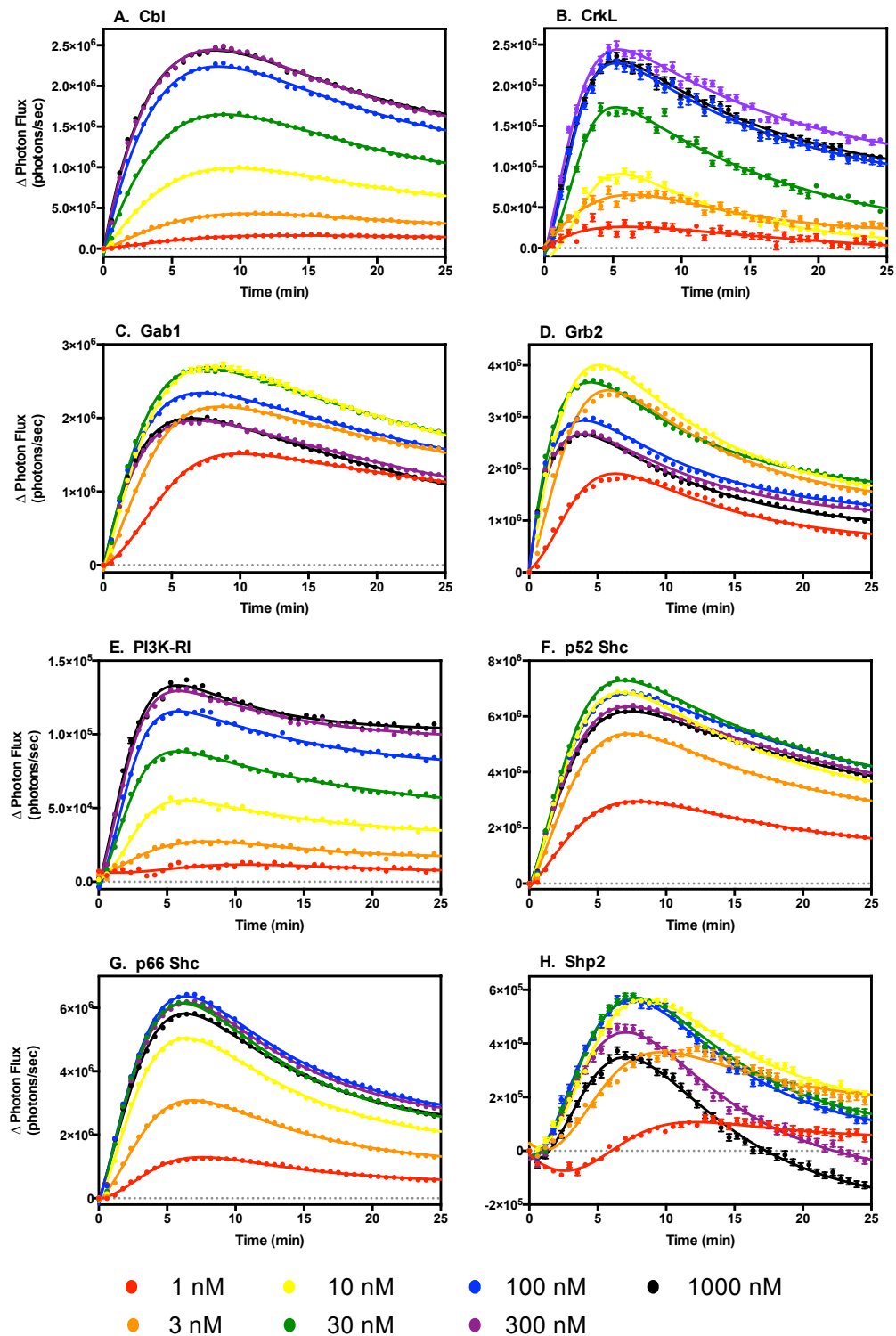
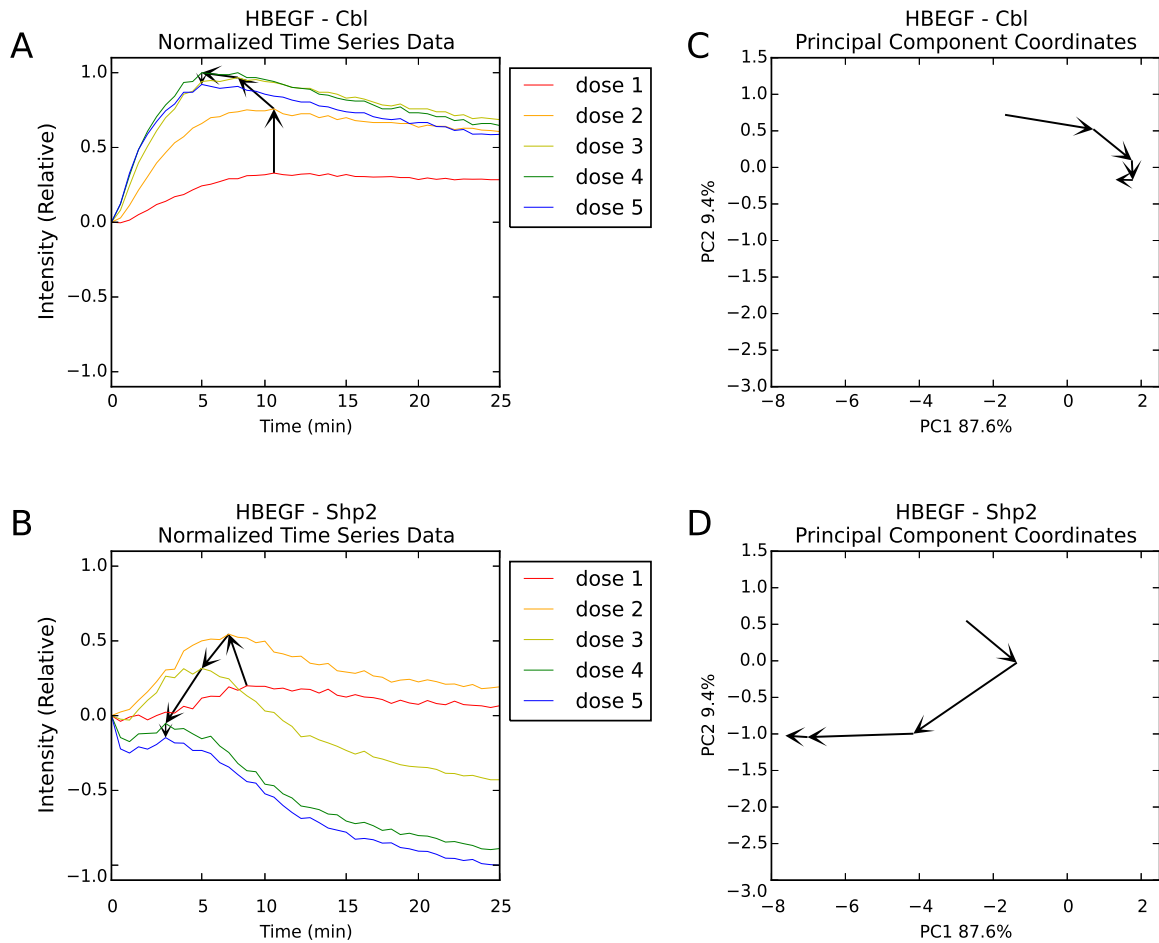


Fig. S6 *EPR-stimulated association of eight signaling proteins with the EGF receptor measured using luciferase fragment complementation imaging.* CHO cells stably co-expressing EGFR-NLuc and the CLuc-fused version of one of eight signaling proteins were assayed for EPR-stimulated light production in the presence of luciferin. Cells were stimulated with the indicated concentration of EPR at time  $t=0$  and light production monitored for 25 min.



**Fig. S . Data in Principal Component Space Correlate with Physical Trends in the Time Series.** The left panel shows normalized time series complementation data for HB-EGF with Cbl (**A**) and HB-EGF with Shp2 (**B**). Superimposed on the plots for the five doses are lines with directed arrows connecting the peak value for each dose, from lowest dose to highest dose. The right panel shows the same time series data but now represented in principal component space, where each point represents an entire curve from the left panel. For both HB-EGF with Cbl (**C**) and HB-EGF with Shp2 (**D**), PC1 correlates highly ( $r=0.97$ ) with the magnitude of the peak at each dose (the peak y-axis value for each dose in the left panel). PC2 correlates highly ( $r=0.90$ ) with the timing of the peak at each dose (the time of each peak from the x-axis of the left panel). Note that the axes are scaled differently and rotated in principal component plots, but the overall shape of the dose response has not changed from the time series to the principal component representation and preserves physical meaning from the time series data.